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Microscale Synthesis of Multi-block Copolymers Using Ultra-fast-RAFT Polymerization

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We demonstrate Ultrafast RAFT in presence of air can be scaled down to 2 µL using microvolume inserts typically used for SEC/HPLC analysis, as a polymerization vessel. By careful cooling and mixing of the sequential monomers, well-defined pentablock copolymers were successfully generated with a total volume of 10 µL.

Scaling down reactions is paramount importance in order to explore enormous number of possible permutation of parameters involved in a chemical synthesis.[1] Polymerization in standard chemistry laboratory reaction vessels becomes increasingly difficult at increasing smaller scales. Transfer of advanced polymer synthesis techniques to smaller scales will allow for the high-throughput screening of polymer composition for biomaterial discovery and previously exploited by step growth polymerisations.[2, 3] However low scale-screening using controlled polymerizations methods was only recently achieved by Boyer *et al* to investigate the influence of polymer architecture on materials properties.[4, 5]

Typically polymerizations are carried out with reaction volumes between 50 mL and 0.5 mL,[6-14] as these ranges are practical for the conventional reaction vessels and deoxygenation processes necessary for typical Reversible Deactivation Radical Polymerization (RDRP). Note that, the latter condition limits scales of the reactions, as using nitrogen sparging or freeze pump thaw cycles to deoxygenate the reaction media is not practical at ultralow volume, due to inherent loss of volatile monomer and solvents. Hence oxygen tolerant RDRP protocols are necessary to allow polymerizations to be carried out at microscale. To this end, Boyer et al have performed ultralow volume reactions (20 µL) in 96 well plates, using photo-catalysed redox Reversible Addition Fragmentation Chain Transfer (RAFT) polymerization without deoxygenation in presence of air.[15] This enabled screening of different homopolymers, diblock copolymers, star architectures and nanoparticles formulations.

Increasingly RDRP protocols without deoxgenation have become an emerging topic,[16, 17] however many of these protocols requires external stimuli,[18] additives[15] or oxygen scavenging enzymes,[4, 19, 20] which deviates from the simplicity of RDRP protocols. To address this, Gody et al. demonstrated standard RAFT polymerization using only conventional ingredients used for RAFT polymerization, without degassing, in vessels open to air.[21] This elegant and simple approach takes advantage of the fast propagation of monomers in water a solvent known to increase the rate of radical polymerization, which is further accelerated at elevated temperatures. This ultrafast RAFT polymerization was generally demonstrated with acrylamide-based monomers with 2,2'-Azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044) as an initiator (10 hr ½ life = 44 °C) and heated to 100 °C, allowing iterative chain extensions to synthesize multiblock copolymers (MBCPs) within 3 minutes per block such that monomer is fully consumed before the initiator is fully decomposed (approximately 80%).[21]

MBCPs are macromolecules with defined control over block sequence and that can be synthesized from just simple chemical ingredients without complex biological machineries, and are amenable to industrial scales.[22-24] The synthesis of MBCPs has been progressed more recently with RDRP, including copper mediated polymerization[25-33] and RAFT polymerization.[34-40] In spite of the inevitable small number of radical termination events, 21 iterative block extensions have been reliably demonstrated with these methods.[41] Furthermore, these routes are popular as they allow incorporation of monomers of various functional groups[42-47] and do not require immaculately dry regents and environment, required for ionic living polymerization systems.[48] Recently, work on sulfur-free RAFT polymerization offers the potential for MBCP synthesis amenable to industrial scales.[41, 49, 50] However, the possible benefits of scaling down MBCP synthesis is often overlooked in academic settings. Industry often relies on the inexpensive small scale

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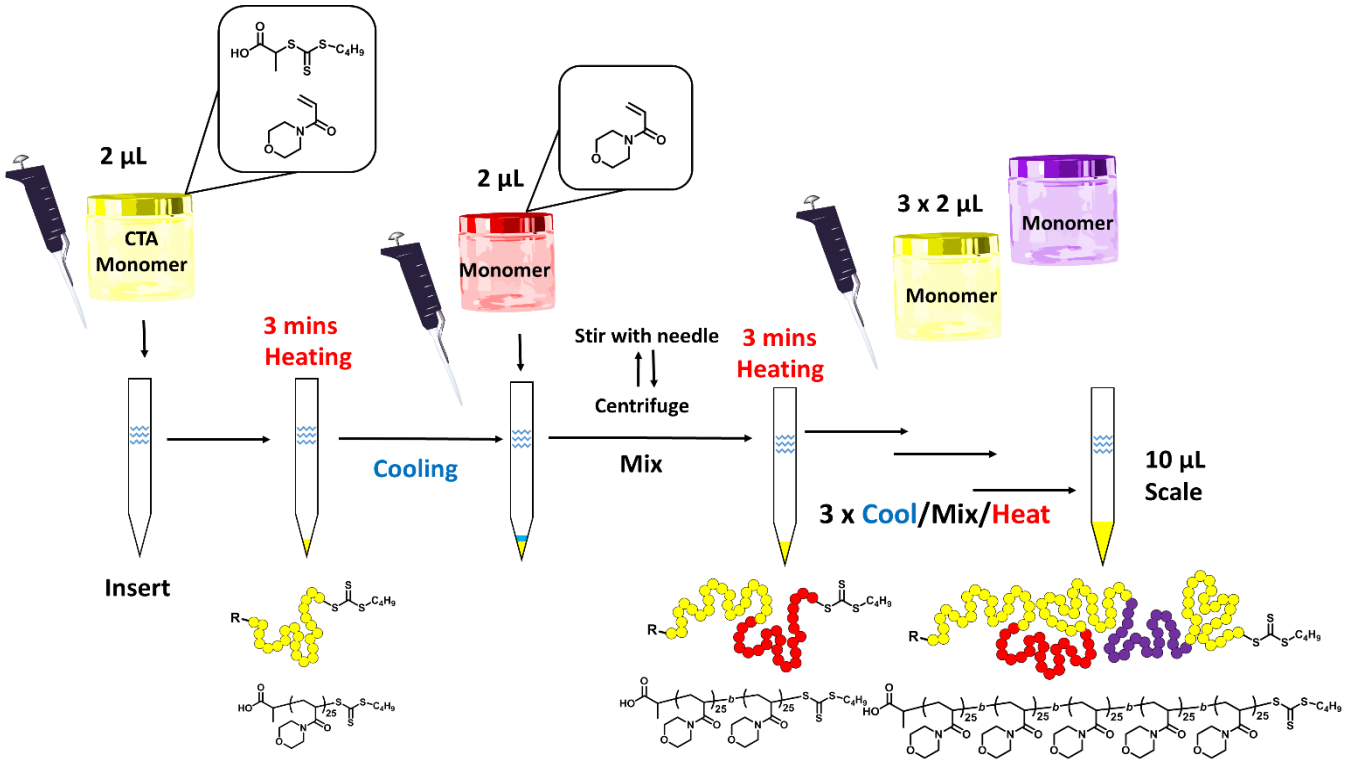

Scheme 1. General scheme: "master mix" (with monomer, CTA, initiator and solvent) is added into the microvolume insert using a regular air displacement micropipettes. After 3 mins of heating at 100 °C in an oil bath polymerisation was complete, the insert was cooled with liquid nitrogen. For sequential chain extension, separate monomer master mix is directly added and mixed by stirring with a needle and centrifugation, before reheating for further 3 minutes for block extension. This cycle was repeated to yield pentablock copolymer. All the polymerisation were carried out without deoxygenation and in presence of open air.

combinatorial reactions or optimisation before larger scale synthesis of the preferred choice or optimized conditions. Microscale MBCP synthesis could have applicability in high throughput microarrays,[1] thus allowing the implications in permutations of monomers and block lengths of MBCPs to be rapidly investigated.

We postulate the aforementioned ultrafast RAFT protocol could be applicable in microliter scale due to the rapid consumption of the monomer without deoxygenation; thus demonstrating the synthesis of MBCPs at a microscale suitable for potential applications such as microarray patterning and combinatorial chemistry with only conventional ingredients for RAFT polymerization.

To counteract the inherent problem of increased air/water interface when scaling down the protocol proposed by Gody et al., we used a narrow micro-volume glass inserts (4.6 mm diameter, 200 µL capacity) with conical bottoms (cone volume = approximately 20 µL) that are typically fitted into a standard 2 mL vials for HPLC/GPC analysis for low volume analyses. A master mix of the RAFT agent, monomer, solvent and initiator was made as "all-in-one" stock solution and added into the insert using a standard micropipette(scheme 1). This mix was made following closely to the published protocol,[21] using VA0-44 as an initiator (3 x 10^{-3} M, $[CTA]/[I]_0$ = 40) and N-acryloyl morpholine (NAM) as suitable acrylamidic monomer ($[M]_0$ = 3 M) in aqueous mixture and 2-(((butylthio)-carbonothioyl)thio)propanoic acid (PABTC) as a RAFT agent. The inserts were then heated in oil bath at 100 °C for 3 minutes. In contrast to the previous study where the temperature of

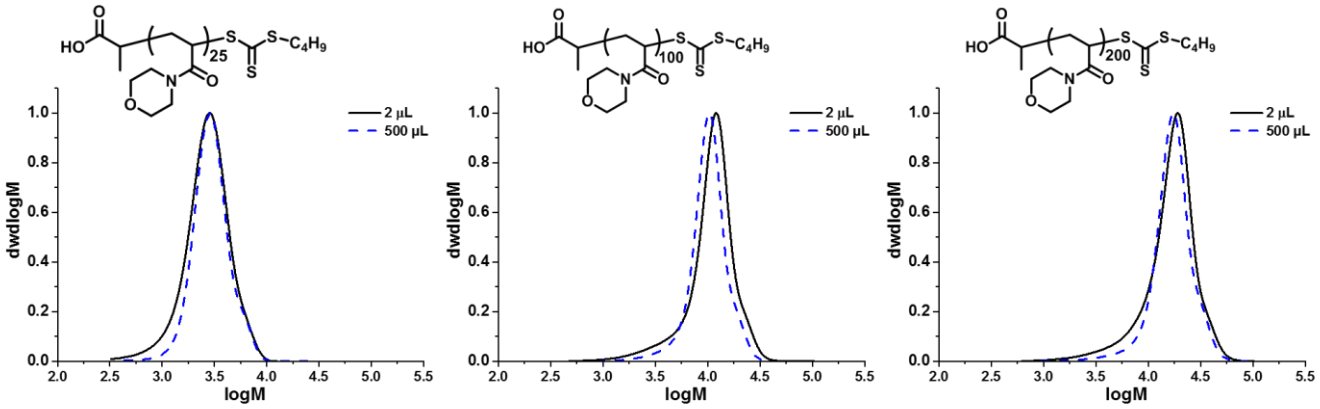

Figure 1. SEC analysis (DRI, $CHCl_3$) of $P(NAM)_n$ (n = 25, 100 and 200) in microscale (2 µL) in microvolume inserts and normal scale (500 µL) in conventional test tubes (5.4 ml). All the polymerization carried out under 3 minutes without stirring, deoxygenation and open to air.

the reaction increase was gradual, taking 80 seconds to reach 96 °C,[21] we assume the temperature of the reaction to reach equilibrium almost immediately. Conveniently as the polymerizations were carried in SEC vial inserts, the reaction mixture was directly diluted with SEC eluent within the insert, and injected directly for SEC analysis (Figure S2). A duplicate reaction was carried out to dilute with NMR solvent (d_6-DMSO) to measure monomer conversion by NMR.

Preliminary experiments were designed to investigate the absolute limit of scale for the solution-based polymerization. Initially this was investigated with a targeted degree of polymerization (DP) of 25 using 20 % dioxane to aid the solubility of the CTA. At 10 µL ($M_{n,SEC}$ = 2200 gmol^{-1}; $Đ$ = 1.23), 5 µL($M_{n,SEC}$ = 2600 gmol^{-1}; $Đ$ = 1.23), and 2 µL ($M_{n,SEC}$ = 2600 gmol^{-1}; $Đ$ = 1.29) we were able to reproducibly obtain $PNAM_{25}$ as observed by SEC analysis (Figure S1) with a slight increase in dispersity at the microliter scale, however comparable to polymerization carried out in 5.4 mL test tubes (termed macroscale in this paper) ($M_{n,SEC}$ = 2700 gmol^{-1}; $Đ$ = 1.19). At 1 µL ($M_{n,SEC}$ = 2600 gmol^{-1}; $Đ$ = 1.42) scale polymers were obtained, but results were not reproducible. The weight loss due to evaporation was also noted (Table S1), which seemingly suggests the effect of evaporation was detrimental at 1 µL scale. Hence we presume that 2 µL is the lower scale limit achievable with this method. Our next objective was to apply this protocol to longer polymer chain lengths of $PNAM_n$ (Figure 1). Increasing the chain length four fold (DP_n = 100), required a slight modification of the master mix (10 % dioxane; $[I]_0$ = 1 x 10^{-3} M, $[CTA]/[I]_0$ = 30). Pleasingly polymerization yielded $PNAM_{100}$ at 2 µL scale ($M_{n,SEC}$ = 9200 gmol^{-1}; $Đ$= 1.36), in contrast to macroscale the molecular weight distributions was relatively broader by SEC analysis ($M_{n,SEC}$ = 8900 gmol^{-1}; $Đ$= 1.19). Increasing the length further (DP_n = 200), increased the dispersity at 2 µL scale ($PNAM_{200}$, $M_{n,SEC}$ = 26800 gmol^{-1}; $Đ$ = 1.43), compared to the macroscale equivalent ($M_{n,SEC}$ = 15000 gmol^{-1}; $Đ$= 1.23). SEC analysis in all cases revealed slightly higher dispersity due to appearance of low molecular tailing. Also the ^{1}H NMR spectra revealed more residual monomer was present (approximately 2-3 % more). As targeting DP of 25 of NAM yielded relatively narrow dispersity at 2 µL scale, we therefore decided to keep this a constant block length for our MBCPs. In order to generate MBCP's through iterative chain extension with the current protocol, it was important to consider the limitation of mixing sequential monomers in the polymerization mixture, as stirring during polymerization is unfeasible at the 2 µL scale. To maximise the mixing of each monomer aliquot the polymerization reaction mixture was cooled prior to addition of new monomer and stirred before heating again at 100 °C for successful sequential chain extension. This circumvented the need for continual stirring during the addition of sequential monomers. Thus by adopting this necessary measure of cooling and mixing before reheating (Scheme 1), we were able to successfully demonstrate successive chain extensions within the insert vials to synthesize a homopolymer in five successive chain extensions, poly($(NAM)_{25}$)$_5$, at 5 µL per block (final $M_{n,SEC}$ = 10600 gmol^{-1}; $Đ$ = 1.25) and 2 µL per block (final $M_{n,SEC}$ = 10000 gmol^{-1}; $Đ$ = 1.31) (Figure 2). Centrifugation was necessary to collect the new monomer solution into the bottom the insert before stirring (see supporting info for full details). It is important to note, that the monomer concentration of the chain extension stock solution was kept constant at 3 M, such that the same DP per chain extension could be targeted by sequentially adding the same volume as the original block. It is noteworthy that all the chain extension stock solutions had contained the same initiator concentration of 2.2 x 10^{-3} M. This was designed to give an overall macroCTA/initiator ratio of 40 constant per block, whilst assuming that 20% of initiator is still

Table 1. The range of (micro)scales, monomer conversion, theoretical and experimental number average molar mass and dispersity of homopolymers and multiblock copolymers synthesized

Polymer	Scale[a] (µL)	Conv.[b]	$M_{n,th}$[c] (gmol^{-1})	$M_{n,SEC}$[d] (gmol^{-1})	$Đ$[d]
$P(NAM)_{25}$	500	> 97	3600	2700	1.18
	10	> 98	3600	2200	1.23
	5	> 98	3600	2600	1.23
	2	> 98	3600	2600	1.29
	1[e]	> 96[e]	3600[e]	2600[e]	1.42[e]
$P(NAM)_{100}$	500	> 99	14000	8900	1.19
	2	> 97	13600	9200	1.36
$P(NAM)_{200}$	500	> 98	26800	15000	1.23
	2	> 98	26800	13000	1.43
$P(NAM)_{25}$ -*b*-$(NAM)_{25}$ –*b*-$(NAM)_{25}$ -*b*-$(NAM)_{25}$-*b*-$(NAM)_{25}$	2500	> 99.9	17200	12600	1.23
	25	> 99	17200	10600	1.25
	10	> 99	17200	10000	1.31
$P(NAM)_{25}$ -*b*-$(DMA)_{25}$ -*b*-$(NAM)_{25}$ -*b*-$(HEAm)_{25}$-*b*-$(NAM)_{25}$	2500	> 96	15400	15100[f]	1.32[f]
	10	> 98	15500	14000[f]	1.35[f]

[a] All polymerizations are carried out in insert vials unless the scale is above or equal to 500 µL are carried out in test tube (5.4 ml). [b] Determined using equation 1 in supporting information. [c] As calculated from equation 2 in supporting information. [d] Determined by SEC with THF as the eluent with PMMA as a calibrant, unless stated otherwise. [e] not reproducible. [f] Determined by SEC with DMF as a eluent with PMMA as a calibrant.

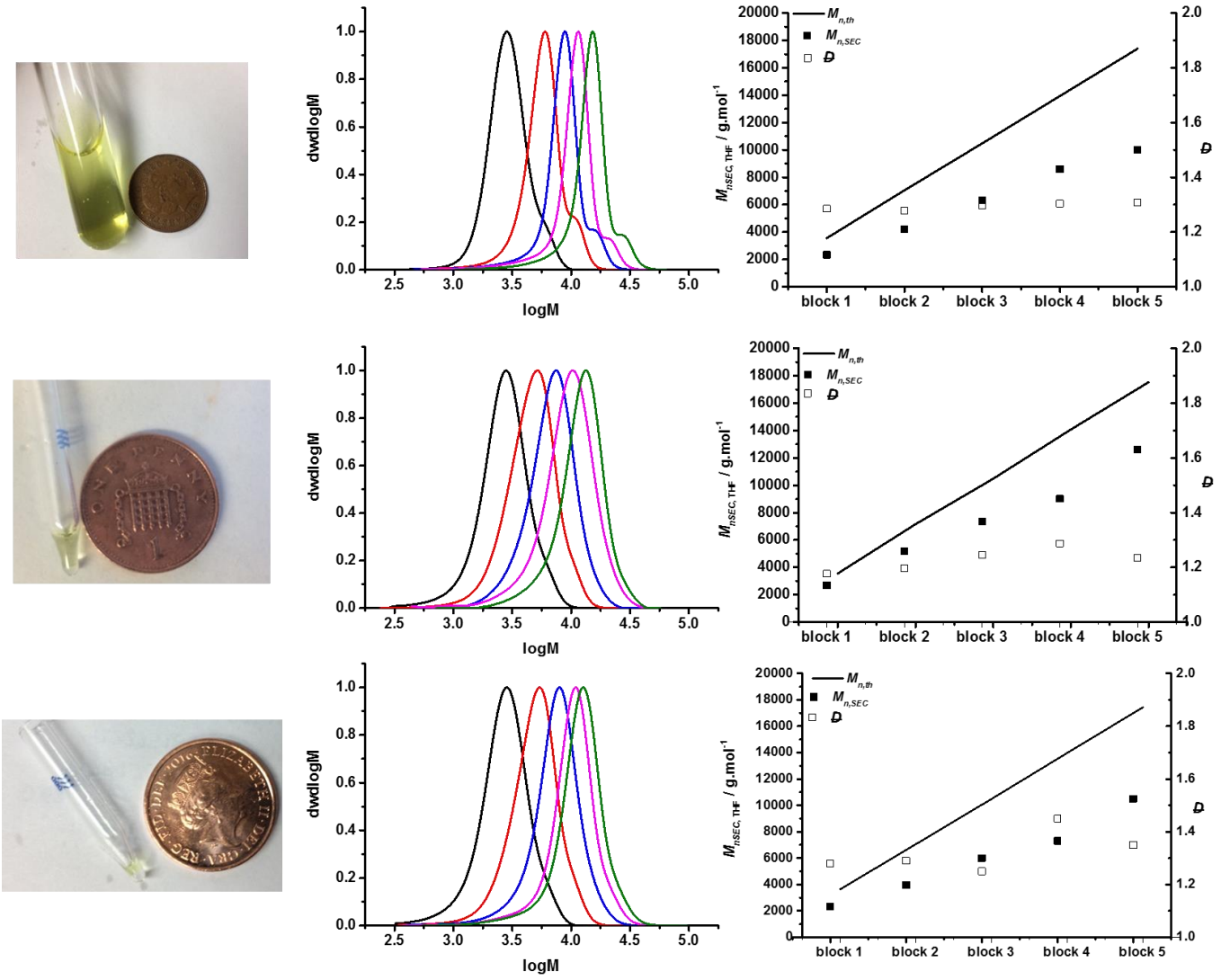

Figure 2. Multichain extension to generate P(NAM$_{25}$)$_5$ synthesis with Ultrafast RAFT polymerization through iterative chain extensions at different scales: Top row = 2.5 ml, 0.5 ml per block; middle row = 25 µL, 5 µL per block; bottom row = 10 µL, 2 µL block. Left Column: Photograph after reaction next to a British penny coin (20.3 mm in diameter) as a reference to the size of the scale. Middle column: SEC chromatograms for successive chain extensions. Right column: Evolution of number-average molar masses and dispersity values with the number of blocks during the preparation of the P(NAM$_{25}$)$_5$. The black line represents the theoretical molar mass calculated from equation 2 (see supporting information). The filled squares represents the experimental molar mass and empty squares represents the dispersity values, both as determined by THF SEC.

remaining from the previous block. This gave a good balance of quantitative monomer consumption (>96%, Table 1) at each block whilst keeping the theoretical livingness of each block high (>98%, see SI for calculation and experimental conditions) to prevent dead chains formed (See table S6-S10 for detailed conditions).

The monomer consumption was followed by ^{1}H NMR spectroscopy and succession of the sequential chain extension was confirmed by GPC analysis of polymerization at each block. To analyze each block extensions, the same number of replicate reactions as the number of iterative blocks was prepared, whereby representative vessel at each stage was used as a whole for each analysis (See Supporting info for detail procedure). In all cases, a linear increase in $M_{n,SEC}$ was observed with increasing number of iterative block extensions (Figure 2), suggesting excellent control in polymerization at microscale. In comparison the molecular weight distributions of P[[NAM]$_{25}$]$_5$ was only slightly broader at microscale compared to macroscale with our protocol (final $M_{n,SEC}$ = 12600 gmol^{-1}; $Đ$ = 1.23). At the macroscale, bimodal distributions were observed, due to back-biting induced β-scission and subsequent branching, with successive chain extensions.[51] Although this is typically characteristic of more labile methine backbone hydrogens of acrylic monomer families, as a result of high temperature this was observed here with an acrylamide monomer. This was indeed the case in previous work which used similar polymer composition, manifest as high molecular tailing.[21] We suspect at the microscale (25 µL and 10 µL), this feature is still present despite molecular weight distributions appearing to be unimodal, due to the broadening of the molecular weight distribution. We attribute this result to an increased interface between air and solution phase when scaling down, subsequently leading to dead chains as result of oxygen related termination

events. It's noteworthy that the weight loss for each chain extension is considerably greater at the microscale compared to the conventional scale (Table S2), however at the 5th block the weight loss was found to be less substantial.

To further demonstrate the robustness of this method MBCPs were synthesized with blocks of different monomers: dimethylacrylamide (DMA) and hydroxyethylacrylamide (HEAm). Pentablock of $P(NAM)_{25}$-*b*-$(DMA)_{25}$-*b*-$(NAM)_{25}$-*b*-$(HEAm)_{25}$-*b*-$(NAM)_{25}$ were prepared in the inserts at the microliter scale (2 µL per block) following our protocol, with well-defined molecular weight distribution ($M_{n,SEC}$ = 14000 $gmol^{-1}$; $Đ$ = 1.35) which was comparable to macroscale synthesis ($M_{n,SEC}$ = 15100 $gmol^{-1}$; $Đ$ = 1.32). Note that the theoretical number average molecular ($M_{n,th}$) of this pentablock gave a good agreement with $M_{n,SEC}$ owing to the DMF used an eluent for the SEC analysis (Figure S4-S5), due to the better agreement of solvation in comparison to PMMA calibrant.

Conclusions

To conclude, we have demonstrated the robustness of oxygen tolerant ultrafast RAFT polymerization at microscale of 2 µL. By careful consideration of monomer mixing we generated well-controlled MBCPs (pentablock copolymer) by iterative addition, with an overall scale of 10 µL without continual stirring. It is important to note the limitation of our methodology is exclusive to acrylamidic monomer families with water as a solvent and targeting short blocks (DP 25) is ideal for iterative chain extensions to retain high livingness. Currently ongoing investigation(s) are in progress to investigate the robustness of the protocol for complex architectures, solvent and applicability in biological science.

Conflicts of interest

The authors declare no competing finical interest.

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